AN ARCHITECTURE FOR REPRESENTING BIOLOGICAL PROCESSES BASED ON NETWORKS OF BIO-INSPIRED PROCESSORS

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***Abstract**: In this paper we propose the use of Networks of Bio-inspired Processors (NBP) to model some biological phenomena within a computational framework. In particular, we propose the use of an extension of NBP named Network Evolutionary Processors Transducers to simulate chemical transformations of substances. Within a biological process, chemical transformations of substances are basic operations in the change of the state of the cell. Previously, it has been proved that NBP are computationally complete, that is, they are able to solve NP complete problems in linear time, using massively parallel computations. In addition, we propose a multilayer architecture that will allow us to design models of biological processes related to cellular communication as well as their implications in the metabolic pathways. Subsequently, these models can be applied not only to biological-cellular instances but, possibly, also to configure instances of interactive processes in many other fields like population interactions, ecological trophic networks, industrial ecosystems, etc.*

***Keywords**: Networks of biologically-inspired processors, Bioinspired Architectures, Computational Models, Natural Computing.*

***ACM Classification Keywords**: F.1.1 Models of Computation - Unbounded-action devices.*

Introduction

Several new lines of research have been initiated in the last decade within Natural Computing from two working perspectives: on the one hand, the bio-inspired architectures and computational models, and on the other, the computational techniques and user friendly tools, which support the advancements in synthetic and systems biology. A Network of Bio-inspired Processors (NBP) [Castellanos, 2003] [Manea, 2005] [Campos, 2012] is a computational model inspired by cell biology; thus it is based on a rather common architecture for parallel and distributed symbolic processing and is related to the Connection Machine [Hillis, 1979] and the Logic Flow Paradigm [Errico, 1994]. NBP model consists of several processors, each one of which is placed in a node of a virtual graph. Every processor acts on local data in accordance with some predefined rules. After that, the processor both sends and receives the data (which behaves like a mobile agent that can navigate in the network following a given protocol). Then, the processors can communicate the data resulting with the rest of the processors which it is connected in the graph, using a filtering strategy. This strategy may require satisfying some conditions that are imposed by processors, when sending, receiving or both. A processor node is very simple: can be either an evolutionary, splicing or genetic processor depending on the operations that carries out. In addition, an extension of NBP named Network Evolutionary Processors Transducers (NEPT for short) was introduced in [Gómez, 2012] to simulate the work of generalized sequential machines.

Changes of the state of a cell can be modeled by means of rewriting rules like in formal grammars [Pâun, 2000]. Also, the parallel nature of these changes implies a parallel application of the involved rules. In this sense, is

more than proved that NBP is a suitable bio-inspired computing model to represent massively parallel changes of the state of a cell [Castellanos, 2003].

Cellular organization and their biological processes include evolutionary aspects which can be viewed as a complex web of subsystems that transform the matter, such as cellular metabolism, signaling, sexual reproduction, etc. One can consider such a web as a composition of a number of different networks working together. Moreover, each one of these networks will represent the dynamics of a biological process, like the metabolism through metabolic pathways or cellular signaling through intracellular pathways. Therefore, we claim that a web of NBPs and NEPTs is able to represent this dynamic. In addition, we propose a multilayer architecture to design and to build this web of NBPs and NEPTs working in a cooperative way.

Related Work

The main framework analysis for the most part of biological dynamics remains in the theory of ordinary differential equations (ODE). There are a lot of works approximating ODE models to particular biological phenomena and some of them focus in a more general perspective, for instance the works introduced in [Schaff, 1997] and [Novak, 2006]. However, the use of this type of models presents some intrinsic limitations in the evaluation of the kinetic reaction rates, which usually refer to a microscopic level, hardly accessible to reliable measurements. Really, in living organisms, these measurements dramatically alter the context of the investigated processes [Manca, 2009]. On the other hand, in a discrete mathematical setting, specific applications for modeling biological phenomena and bio-inspired paradigms are widely developed. Bio-inspired paradigms abstracted from the information processing that are present in all living cellular systems, such as Membrane Computing based on P Systems [Pâun, 2000] have demonstrated being universal and computationally complete when they work in a massively parallel way. In particular, P Systems have exhibited models representing biological phenomena. However, these models are mainly of a qualitative nature, and do not provide criteria for predicting quantitative aspects of biological processes. For overcoming these limitations, Metabolic P (MP) systems were introduced in [Manca, 2009] and then widely developed along different approaches. Nevertheless, the extension of these models to other types of biological processes is still an open working line, despite of the efforts given in [Gutiérrez, 2008] and [Nguyen, 2009], mainly due to the hierarchical structure of P Systems and the limitations to develop suitable and practical architectures (both software and hardware) to implement them.

NBP were widely studied from its definition [Castellanos, 2001], as well as a series of subsequent works about their computational power and complexity. NBP can be viewed as a device that solves NP-complete problems in linear time with polynomially bounded resources. In addition, a new variant of NBP with the same properties (but without filtering process) and an energetic charge representation was studied in [Alarcón, 2012]. Also a software environment and its architecture were presented in [Ortega, 2012]; this framework continues to be an active line of research as well as the suitability of some hardware architectures. Recently, in [Gómez, 2012], it has been proved that a transducer based on the model denominated NEP transducer (NEPT) can simulate the work of generalized sequential machines, that is, every recursively enumerable language can be the transduction defined by the new transducer of a very simple regular language, computing the set of all words obtained by the shortest computations.

So far, NPB had only been used as solvers of classical mathematical problems. Alike that the other discrete computational models, NBP can be investigated as solvers of other real problems, not only those related to biological interest, but also the possible relevance ecologies, dynamics of social interactions, etc., that are more complex than combinatorial optimization, as well as other classical NP-complete ones. The study of the web structure of a NBP together the definition of its communication process, as well as some aspects concerning computational power, efficiency and descriptive complexity leads to interesting results that apply in new fields.

Contributions

In this work we present two main contributions. The first one is the use of NEPT to model some chemical transformations within cell biological phenomena. In particular, this novelty is applied to simulate chemical transformations of substances within a computational framework. We use a NEPT to transform words representing extracellular signaling molecules in new words representing receptor proteins able to start the signaling activities. These new words define a language that is recognizable by a NBP. The second contribution, and related to the first, is the definition of an architecture that utilizes both NBP and NEPT to represent signaling activities associated with cellular metabolism. Signaling activities start when an extracellular signaling molecule arrives at plasma membrane where are transformed for receptor proteins. This transformation gives as result intracellular signaling proteins responsible to activate one or more signaling pathways. Finally, one or more of the intracellular signaling proteins alters the activity of effector proteins and thereby the activation or inhibition of specific processes that modify the behavior of the cell, among themselves the metabolism. NEPT transformations represent the first level in our multilayer architecture. The rest of signaling activities are modeled by specific architecture layers, as is extended in section *Architecture Proposal*.

Structure of the rest of the paper

In section "*Definitions and basic Concepts"*, concepts related with the NPB model and its extension as well as a brief biological background are introduced. Section "*Architecture Proposal"* contains the definition of the architecture proposed and its motivation. Section "*Using our architecture"* illustrates the representation of one instance of specific biological processes, such as the Krebs cycle and the MAS shuttle pathway, using our architecture and, finally, the last section shows the conclusions and future work.

Definitions and basic concepts

NBP model concepts

A Network of Bio-inspired Processors (NBP) consists of several processors, each one of which is placed in a node of a virtual graph. Each processor node acts on local data in accordance with some predefined rules. The data becomes a mobile agent which can navigate in the network following a given protocol. The data travel between nodes by means of a filtering process only. Note that this process may require to satisfy some other conditions that are imposed by the processors when sending or receiving data (even simultaneously), by using a variety of filtering strategies. A processor node is very simple; it can be either an evolutionary, splicing or genetic processor taking into account the operations that carries out:

- An *evolutionary processor* performs very simple operations, namely, point mutations in a DNA sequence (insertion, deletion or substitution of a pair of nucleotides). This type of processor is only specialized for just one of these evolutionary operations. More generally, it can be viewed as a cell that contains genetic information encoded in DNA sequences which may evolve by point mutations. A network containing this type of processors is denominated *Network of the Evolutionary Processors*.
- A *splicing processor* performs the operation of recombination, which is presented in form of splicing. This operation is one of the basic mechanisms by means of which, DNA sequences are recombined under the effect of enzymatic activities. A network containing this type of processors is called it *Network of the Splicing Processors*.
- A *genetic processor* has two operations: (1) *Mutation* between symbols (similar to the substitution operation in the evolutionary processors) and (2) *Pure and massive crossover* (similar to the splicing

operation by taking empty contexts). These processors become part of a *Network of the Genetic Processors*.

In addition, there exists another type of processor called *polarized processor* [Alarcón, 2012], which is a special type of evolutionary processor having a valuation mapping. This mapping represents the polarization of the processor in terms of an electrical charge: positive, negative or neutral, which is useful for modeling some biological properties as the inhibition or activation of the molecules or processes. A NBP having this type of processors is denominated *Network of Polarized Evolutionary Processors* (NPEP). For a more detailed view about all of the above networks, we refer the reader to [Castellanos, 2003] [Manea, 2005] [Campos, 2012].

Since a NBP is intended to be used as an universal problem solver, an important aspect is the part of encoding the instance of the problem and that of decoding the solution. It is natural to ask that these steps to be accomplished by a mechanism based on a particular NBP, the NEP as well. Then, we are going to consider a transducer based on the NEP structure which is formed by a directed graph whose nodes are evolutionary processors without filters. In [Gómez, 2012] is demonstrated that these new type of transducers, denominated NEPT, can simulate the work of generalized sequential machines (gsm), computing the set of all words obtained by the shortest computations. Unlike the case of gsm every recursively enumerable language can be the transduction defined by the new transducer of a very simple regular language. The computation on an input word starts with this word placed in an input node and halts as soon as the output node is nonempty. Therefore, a NEPT translates the input word into a set of words existing in the output node. Accordingly, they add new capacities at the NBP, allowing the extension of the model. As the novelty that we have introduced in the section *Introduction*, we use NPET as an overlay network that translate an input into a language that can be recognized by one or more NBP working as underlying networks.

Biological concepts

Cellular communication is a biological process that enables a cell to send chemical signals across the extra-cellular environment, allowing the molecular interchange between cells. Complex intracellular mechanisms are needed to control what signals are emitted and at what time, in order to enable the signal-receiving of the cell. These signals are interpreted and used to guide the behavior of the cell in question. A communication process begins with an extracellular-signal molecule, which arrives at the plasmid membrane. This molecule is received by a molecular receptor, which in turn, activates one or more intracellular signaling pathways. Within these pathways, there are relay chains of molecules (mainly intracellular signaling proteins) that process the signal and distribute it to the appropriate intracellular targets. Targets are generally effector proteins, which are activated (or inactivated) by the signaling pathway. They alter the cellular behavior through processes affecting the shape, movement, metabolism and gene expression, as it shown in Figure 1-(b). Many intracellular signaling proteins behave like molecular switches. When receiving a signal, they switch from an inactive to an active conformation, until another process switches them off [Alberts, 2008]. In summary, extracellular signal molecule is altered (transduced), amplified, distributed, and modulated *en route* through signaling pathway (see Figure 1-(a)). In this sense, activities in the top of communication process, like transduction and amplification, can be modeled by a network (within a given web) that works as *overlay network*. This concept is relevant because of it defines the first level in our multilayer architecture as we will see in the next section.

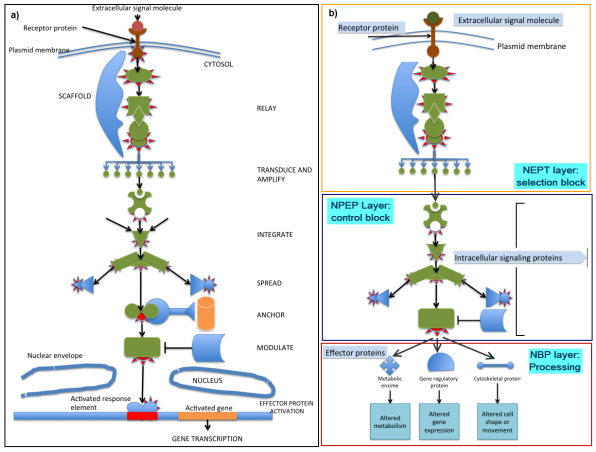

Figure 1: Architecture model of a cell communication process. a) Cell communication process. From receptors to the nucleus through intracellular signaling pathways (adaptation of [Alberts, 2008]). b) Architecture model showing NEPT, NPEP and NBP layers.

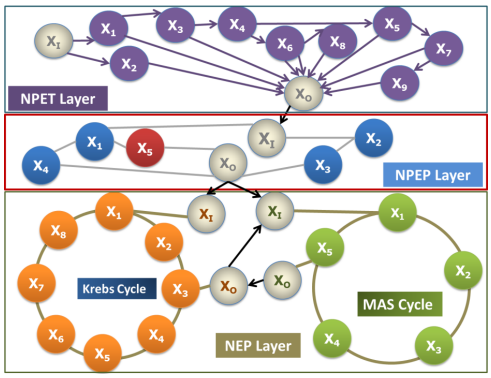

Figure 2: Multilayer architecture to simulate signaling by calcium, MAS and Krebs cycle (X_i represents the nodes of the respective network).

Architecture proposal

As we said before, a NEPT translates input words into a language that can be recognized by one or more NBP. We will see this NEPT as an *overlay network*, that is, a virtual network built on top of one or more existing networks (called the *underlying network*). The overlay network adds an additional layer of indirection/virtualization and changes properties in one or more areas of the underlying network. We propose that the activities in the top of a communication process (of a cell), like transduction or amplification, are modeled by a NEPT working as an *overlay network*.

In this context, our second contribution (see section *Introduction*) is the definition of an architecture for representing the signaling of a cell from reception until the activation of a target processes. We propose three blocks of computing (see Figure 1-(b)):

1. ***Selection***: represents the reception of an extracellular signal molecule arriving at the cellular membrane, and its alteration (transduction), amplification and distribution through of the adequate signaling pathway selected by the cell.
2. ***Control***: realizes the monitoring functionality of signaling pathway either activates or inactivates the target proteins (effectors) in order to unleash the respective cellular processes.
3. ***Processing***: represents the target activity which alters the cellular behavior, like shape, movement, metabolism and gene expression.

Our architecture is inspired in these three blocks, and associates each one of them with its corresponding layer. Each layer is modeled by a specific type of NBP (including NEPT), namely:

- **Top layer (overlay network):** it corresponds with the *selection* block of computing and is implemented by a NEPT.
- **Middle layer (controller network):** it corresponds with *monitoring* block of computing and is implemented by a NPEP.
- **Bottom layer (underlying network)**: it corresponds with *processing* block of computing, and is implemented by one or several NBP.

Using our architecture for modeling metabolic processes

Within the eukaryotic cell, hundreds of different protein kinases are organized into complex networks of signaling pathways that help to coordinate the cellular activities in a cooperative and involved manner. A very well-known metabolic process is the Krebs cycle, also called tricarboxylic acid cycle or simply acid cycle, which is critical in cellular respiration. One of the target activities of the Krebs cycle is the generation of energy. This energy is produced by a chain of reactions, some of them, controlled by calcium (also by the ion Ca^{2+}). The signaling by calcium helps to activate other metabolic processes, such as the malate-aspartate shuttle pathway (MAS for short). In fact, MAS and the Krebs cycle share common enzymes, and major target activity altered by Ca^{2+} is related with brain stimulation. These metabolic activities are of great interest in the brain research [Contreras, 2009]. We use our architecture to design the process of signaling by calcium and the relationship between the Krebs cycle and MAS as follows (see Fig. 2):

- **NEPT layer**: in this overlay layer, we define one NEPT which is able to receive different strings representing extracellular signaling molecules, and translate them into others representing receptor proteins (i.e. piruvate, calcium). These proteins can be recognized by some underlying NBP in the bottom layer, allowing to restart the Krebs cycle and MAS respectively.
- **NPEP layer:** in this control layer, we define only one NPEP. This network selects the respective pathway (represented by a NBP in the bottom layer) depending on the string that represents the adequate receptor traduced by NEPT. Also the NPEP is responsible either to activate or inhibit these networks through the model of the effector proteins function.
- **NBP layer:** in this underlying layer, we define two NBP that represent the Krebs cycle and the MAS pathway respectively. Both networks are communicated by means of the their input/output nodes, and they also compete by the enzymes necessaries for their internal processes, as well as the ketoglutarate, the nicotinamide adenine dinucleotide (in reduced NADH and oxided NAD+ forms), malate, etc. Both networks share the intracellular environment, where the before enzymes are located as well as other type of molecules such as proteins, metabolites, etc.

Conclusions

We have proposed as novelty, the use of NEPT to model some biological phenomena to simulate chemical transformations of substances within a computational framework. In addition, up to our knowledge, we have defined the first multilayer architecture that uses both NBP and NEPT to represent biological processes, for instance, signaling activities that involves cellular metabolism.

Currently, we are working in the modeling and simulation of some interrelated biological phenomena. In particular, we use our architecture to model the Krebs interplay between these processes sharing and competing for substances is an important study of the brain stimulation in vivo as was demonstrated in [Contreras,2009]. We consider important modeling these processes using our architecture, in order to develop a computational software framework that allows their computational simulation. Finally, the analysis of specific features coming from the interaction of a web of NBP and NEPT is a new line of research to be explored in many other fields. In particular, by using our extensible and reconfigurable architecture.

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